

GM Leung 梁卓偉  
LM Ho 何禮明  
TH Lam 林大慶  
AJ Hedley 賀達理  
JSM Peiris 裴偉士

# Prevalence of SARS-CoV antibody in all Hong Kong patient contacts

## Key Message

The near absence of transmission (seroprevalence=0.19%) resulting in asymptomatic infection in this representative high-risk group of close contacts indicates that the prevailing SARS-CoV strains in Hong Kong almost always led to clinically apparent disease.

## Introduction

Since the SARS outbreak, considerable progress has been made in understanding the biology, pathogenesis, and epidemiological features of both the coronavirus and the disease. Epidemiological studies of hospitalised patients suggest that the overall transmissibility of SARS (as indicated by the basic reproductive number  $R_0=2.7$ ; 95% confidence interval [CI], 2.2-3.7) is relatively low compared with other pathogens.<sup>1</sup> However, such studies could not take into account possible episodes of mild or moderate illness that did not resort to inpatient care and could not address whether asymptomatic community spread played a role in the 2003 epidemic. If this type of spread occurred, sufficient herd immunity against SARS-CoV to protect against another large-scale outbreak might have developed in the population. The full spectrum of disease associated with SARS-CoV infection should be examined to define more precisely what constitutes a case requiring quarantine and isolation to minimise potential human-to-human spread. Understanding these issues requires the systematic study of the seroprevalence of SARS-CoV antibody in a large sample stratified by age and other baseline characteristics, especially since children were disproportionately less affected by SARS, both in terms of reduced incidence and severity of infection. Serological surveys can be based on a random sample from the total population with appropriate stratification, on serum collected for other reasons (eg blood donors, all hospital admissions), or on surveys of persons who resided in sites of superspreading events or who have had close contact with a confirmed SARS patient.

We report a serological survey for immunoglobulin G (IgG) against SARS-CoV in a representative sample of close contacts of all SARS patients in Hong Kong (>76% had laboratory confirmation of SARS by either paired serology or repeat reverse transcription-polymerase chain reaction [RT-PCR] according to World Health Organization [WHO] criteria).<sup>2</sup>

## Aims/objectives

To estimate the seroprevalence and associated predictors of SARS-CoV IgG antibody among all close contacts of the case cohort during the Hong Kong 2003 outbreak.

## Methods

During the epidemic (from 15 February to 22 June 2003), close contacts were prospectively identified by the Department of Health through standardised telephone interviews with all 1755 confirmed SARS patients within 1 week of hospital admission. A close contact was defined as a person who had cared for, lived with (in the same household), or came into direct contact with body fluids of the SARS patients within 10 days before hospital admission. A total of 3612 close contacts were recorded; 505 were diagnosed as having SARS. Of the remaining 3107 contacts, 2805 (90%) had a telephone number available, as provided by the primary patient. We successfully contacted 2337 (83%) of the contacts from 23 October to 30 November 2003, and 1776 (57% of those eligible) consented to a telephone interview after the purpose of the study was explained to them by trained public health nurses. The interview consisted of questions that assessed the relationship between the patients and contacts; the timing, intensity

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Department of Community Medicine, The University of Hong Kong, 21 Sassoon Road, Pokfulam, Hong Kong SAR, China  
GM Leung, LM Ho, TH Lam, AJ Hedley  
Department of Microbiology, The University of Hong Kong, Queen Mary Hospital Compound, Pokfulam Road, Hong Kong SAR, China  
JSM Peiris

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Principal applicant and corresponding author:  
Prof GM Leung  
Department of Community Medicine, The University of Hong Kong, 21 Sassoon Road, Pokfulam, Hong Kong SAR, China  
Tel: (852) 3906 2000  
Fax: (852) 3920 1945  
E-mail: gmleung@hku.hk

and frequency of contact; precautionary measures adopted during contact with the patient; known contact with other SARS patients; clinical symptoms of febrile, respiratory, gastrointestinal, or constitutional illness since February 2003; medical and travel history; and sociodemographics. Participants were then invited to provide blood samples for serological testing. Shopping coupons (worth US \$25) were given to participants after blood was collected as compensation for time and travel costs.

Samples were screened by the Government Virus Unit of the Department of Health by using viral lysate enzyme-linked immunosorbent assay (ELISA; GBI Biotech, Beijing). Positive results were confirmed with immunofluorescence assay (IFA) and neutralisation tests. For the IFA, microscope slides coated with SARS-CoV-infected FRhK4 cells were incubated with serum samples at serial two-fold dilutions starting from 1:25. A positive test was indicated by cytoplasmic fluorescence under ultraviolet microscopy. Using IFA as the standard, the ELISA detects antibody with IFA titre of >25 (ie sensitivity of 100%) and has a specificity of 95%. Neutralisation tests were performed by standard virological methods with Vero E6 cells and SARS-CoV isolate 6109. A titre of >10 was considered positive. The reported sensitivity of 100% was for convalescent-phase serum samples taken a few weeks after the onset of infection in SARS patients, which should apply to our study. During the early phase of infection, IgM predominates; the ELISA kit we used detects IgG only. Therefore, the sensitivity was 80 to 90% (depending on the number of days after illness onset when the serum samples were taken). However, this sensitivity should not have affected our findings, which were based on tests carried out at least 6 months after the last reported case of SARS in Hong Kong.

## Results

Of the 1068 samples analysed, two (0.19%; 95% CI, 0.02–0.67%) contacts had a positive titre (1:25 to 1:50 on IFA compared with at least 1:100 in most recovered SARS cases) for SARS-CoV IgG antibody. None of the two contacts with a positive sample reported a chronic medical condition or being sick with febrile or respiratory illness from February to August 2003. Both seropositive contacts arose from two superspreading events in Hong Kong, ie Prince of Wales Hospital nosocomial outbreak and Amoy Gardens community outbreak.<sup>1,3</sup> The former reported one other close contact, who was interviewed but declined to be tested. The latter was separately identified by three intrafamilial index patients, all of whom lived in the same household and reported only each other as close contacts. The participants who consented to testing were broadly similar to those who declined, except that the former group had relatively fewer children and comprised fewer men. However, those who consented to testing were more likely to report more frequent contact and closer relationships with SARS patients, more febrile or respiratory illness episodes

since February 2003, and a travel history to SARS-affected regions, which may have biased our seroprevalence estimate upwards.

## Discussion

The extent of seropositivity in close contacts of confirmed patients should provide the upper limit of SARS-CoV antibody seroprevalence in the general population, given the relatively intense exposure of these persons to SARS patients. Our finding of the near absence of transmission resulting in asymptomatic infection in this representative high-risk group of close contacts indicates that the prevailing SARS-CoV strains in Hong Kong almost always led to clinically apparent disease. Whereas some SARS patients (especially health care workers) might have been promptly admitted to hospitals, so that transmission to family members was reduced. Almost all SARS patients (perhaps with very few exceptions in children) had severe disease resorting to inpatient treatment; thus, infection with SARS-CoV almost always caused severe disease requiring hospitalisation.<sup>4</sup>

Although our results suggested that SARS-CoV was a new virus in humans without a close precursor or an antigenically related virus that would have induced at least a small degree of cross-reactivity on serological testing, a recent study on a select group of 938 healthy Hong Kong adults (whose serum had been stored as part of a hepatitis B serosurvey in 2001) indicated that 1.8% of the sample had acquired a SARS-CoV-related virus infection at least 2 years before the 2003 SARS outbreak.<sup>5</sup> The investigators speculated that the virus that affected these healthy, seropositive persons was antigenically closer to the recently isolated animal SARS-CoV-like virus than human SARS-CoV, but interspecies transmission from animals to humans was likely to be inefficient, as the virus might not have adapted in the new host.<sup>3</sup> This hypothesis may explain why only a few persons became infected but were asymptomatic. This hypothesis would be compatible with the presumed asymptomatic infection observed in Guangdong animal traders, especially in those who handled masked palm civets, who had a seropositivity rate of 72.7% (95% CI, 49.8–89.3%) in the absence of prior overt clinical disease.<sup>6</sup>

The limitations of the study included incomplete contact tracing (especially in the earlier parts of the epidemic) and potential recall bias (under-reporting of contacts by some patients who were too sick to answer questions). Another possible shortcoming was the lack of a survey of close contacts whose telephone numbers were not provided, although there was no reason to suspect they had a systematically different serological profile. In fact, these were mostly non-household contacts who would have had less intense exposure to SARS patients. In addition, because peak infectivity, as indicated by viral load, usually occurred during week 2 of illness, when most of the patients would

have been isolated in hospital (the mean symptom onset-to-admission interval decreased from a maximum of 9.3 days in late February to 1.0 day by mid-May). Transmission to close contacts in the later stages of the epidemic was therefore less likely.<sup>7,8</sup> Finally, contacts who refused to participate (n=561) or undergo serological testing (n=708) might have been due to their concerns about having SARS (possibly because of having SARS-like symptoms) and did not want to be identified and stigmatised as having been infected with SARS-CoV. Surveys in other countries with large-scale outbreaks such as Canada, China, Singapore, and Taiwan should be undertaken to confirm our findings.

## Conclusions

The near absence of transmission resulting in asymptomatic infection in this representative high-risk group of close contacts indicates that the prevailing SARS-CoV strains in Hong Kong almost always led to clinically apparent disease. It is inferred that infection with SARS-CoV almost always caused severe enough disease requiring hospitalisation.

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